--26. The vaccine according to Claim 10 wherein said polypeptide comprises a mixture of glycoproteins.--

--27. The vaccine according to Claim 20 in which said mixture comprises glycoprotein C and glycoprotein D.--

--22. The vaccine according to Claim 20 wherein said mixture comprises glycoprotein D and additional effective glycoprotein.--

--23. The vaccine according to Claim 22 wherein said mixture comprises glycoprotein B and glycoprotein D.--

***REMARKS***

The Commissioner is authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-1300 (Our Order No. A-54528-9/WHD).

We open with an accounting of the amendments made above with respect to the present specification. These amendments to the specification mirror those made originally in an application in the parental lineage of the present application, namely, USSN 07/814,243 filed 23 December 1991 via the vehicle of an amendment filed by mailing therein on 19 April 1993. It was there characterized and herein mimicked that these amendments to the specification correct patent, minor errors mostly of typographical character. The lineage of the parental stream of priority on page one of the present application is likewise corrected.

In addition, the foregoing amendments include those particularly singled out by the Examiner in Paragraph 15 of Paper No. 4, for which we thank the Examiner.

The claims herein have been amended to remove certain claimed subject matter, and focus on claims that are directed to the embodiment hereof comprising the feature of a vaccine based upon a truncated, membrane-free derivative of a membrane-bound polypeptide of the herpes simplex virus. Obviously, no new matter is involved as all currently claimed subject matter is fully set forth in the specification - see for example, each of pages 5 and 48, from line 5 on.

We note the comment with respect to the figures in Paragraph 16 of Paper No. 4 and intend to comply with such outlined requirements when there is in hand an indication of allowable subject matter.

With respect to Paragraph 17 we believe the claims are now properly cast. Objection was made to Claims 5, 6 and 18 as being in improper form. These claims are amended accordingly; therefore the comment with respect to the Examiner's view as to dependency is mooted.

With respect to the rejection of claims under 35 USC 101, we note that via the amendments to the claims herein, as well as the other two applications for which responses to official actions are filed concurrently, we have removed any provision that would prompt a repetition of such a rejection.

With respect to Paragraph 19 of Paper No. 4 relating to the provisional rejection under the "judicially created doctrine of obviousness-type double patenting", we could take issue as it could be considered that the respective claims in each of these three cases, as amended, are directed to separate patentable inventions under the provisions of 37 CFR 1.601(n). Should the Examiner retain this view, Applicants would consider the filing of an appropriate terminal disclaimer sanctioned by 37 CFR 1.321.

***The Rejections under 35 U.S.C. § 112, Second Paragraph (Paragraph 20 of Paper No. 4)***

Claims 1 to 19 stand rejected under 35 U.S.C. § 112, second paragraph, for purportedly "failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention". Specifically, the Examiner states that "the claims are indefinite in the recitation of "antigenic determinant" because it is unclear what applicant intends". We traverse, of course.

Applicants note that each time the phrase "antigenic determinant" is used in a claim herein, it is immediately followed by the phrase "capable of raising neutralizing antibodies". As such, Applicants submit that one of ordinary skill in the art would readily understand the term "antigenic determinant" to mean a structural portion of a molecule which is recognized by the immune system of a host and against which, as a result of this immune recognition, complementary antibodies are produced. In

fact, this is clearly the definition of "antigenic determinant" which is well-accepted and understood in the art.

Moreover, the term "antigenic determinant" is used throughout the specification consistent with this well-accepted definition. For example, the Examiner is directed to page 5, lines 16-18, which states:

> "the present invention involves a vaccine comprising a polypeptide with antigenic determinants capable of specifically raising complementary antibody..." (Emphasis supplied).

Finally, the Examiner provides absolutely no indication or guidance as to what, other than the well-accepted and understood definition described above, the term "antigenic determinant" could mean. No other possible definition of the term is readily apparent to Applicants.

Next, the Examiner states that Claim 6 is indefinite "because it is not clear whether or not applicant intended the word "at" to be deleted or [sic; from] the terminology "at least one" from the claim." Applicants traverse.

Upon a reading of Claim 6, anyone should recognize that deletion of the word "at" from the phrase "at least one" would render that phrase incomprehensible. As such, Applicants clearly did not intend to delete the word "at" from said claim. The mark which appears over the word "at" in Claim 6 is believed to be merely an artifact from the machine copying of that page and is not indicative of any intention to delete the word from said claim. Therefore, Claim 6 should be read with the word "at".

Finally, the Examiner states that "Claim 13 is indefinite because it is unclear whether or not applicant intends the truncated polypeptide to contain amino acids 1-300". Applicants traverse.

Claim 13 recites that the truncated derivative comprises the N-terminal region of the gD polypeptide up to about amino acid 300. Clearly, this recitation is intended to cover polypeptides beginning with amino acids 1 and extending through about amino acid residue number 300. The term "about", which is routinely and regularly employed in patent claim language, clearly means that the polypeptide can terminate at any amino acid residue which is adjacent to or near amino acid residue 300, from amino acid residues 298 to 302 for example. Certainly, therefore, the recitation in Claim 13 is intended to cover truncated forms of the polypeptide containing amino acids 1-300, as well as other "about" equivalents. We believe the claim language to be clear and concise, and therefore, not indefinite.

***The Rejection under 35 U.S.C. § 112, First Paragraph (Paragraph 21 of Paper No. 4)***

Claims 1 to 6, 8 to 10, 12 and 14 to 17 stand rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is purportedly enabling "only for claims limited to a vaccine comprising a membrane associated and truncated form of the herpes simplex glycoprotein D and a method of

producing the herpes simplex glycoprotein D vaccine." Applicants respectfully traverse.

Initially, the Examiner states her view of the term "pathogen". This is not applicable to the claims as amended herein.

The Examiner next states that "the specification lacks sufficient guidance and teaching to enable the use of the glycoprotein C from herpes simplex virus". In support of this contention, the Examiner cites the specification at page 46 which states:

> "[w]hile the function(s) of gC and gF is at present unknown, and while viable gC minus mutants of HSV-1 have been isolated in vitro (65), it is not clear that either gC or gF are indispensable to the viruses during in vivo infection of the human host and the establishment of latency."

We traverse the rejection.

Initially, Applicants point out that the statement in the specification cited by the Examiner and reproduced above has no bearing on whether glycoprotein C may serve as an effective vaccine. For example, the fact that a particular membrane-associated protein has no known actual function is not indicative of whether that protein presents antigenic determinants against which neutralizing antibodies can be raised. All that is required for glycoprotein C to be effective as a vaccine is that it assists in some manner to elicit host antibodies which bind to and neutralize the virus. Thus, the mere fact that glycoprotein C has no known actual function is irrelevant to whether it may act as an effective vaccine.

The same reasoning applies as to whether glycoprotein C is indispensable to the virus during in vivo infection. If the gC polypeptide both possesses antigenic determinants against which neutralizing antibodies are directed and is expressed on the virus, then neutralizing antibodies will bind to and neutralize the virus, regardless of whether the protein is indispensable for in vivo infection.

Moreover, contrary to the Examiner's assertions herein, the specification at page 5, lines 5 to 11 states:

> "[a]nother specific embodiment relates to another class of glycoproteins obtained by recombinant DNA processes useful as components in a vaccine against HSV-1 and/or HSV-2 viruses. Specifically, such glycoprotein class includes HSV-1 gC (effective against HSV-1), HSV-2 gF (more properly referred to as an HSV-2 gC), effective against HSV-2, or combinations of the two proteins, effective against both viruses. (Emphasis supplied).

Furthermore, the specification at page 47, line 1 to page 48, line 9, provides a detailed description of the HSV glycoprotein C and clearly states:

> "[i]t is believed that the cloned gC-2 glycoprotein may be expressed and formed into a vaccine...It is further believed that a vaccine which includes a mixture of such recombinant gC and gD glycoproteins would be significantly more effective as a vaccine against HSV-1 and HSV-2 than one based upon either glycoprotein alone."

Given the above, Applicants submit that the present specification is enabling for the use of glycoprotein C as a vaccine against herpes simplex virus. In light of this disclosure, Applicants respectfully request withdrawal of the outstanding rejection.

With respect to paragraph 22 of Paper No. 4, Applicants take vigorous issue with the position taken by the Examiner. The Examiner supposes that certain subject matter specified by certain of the claims, listed under parts a) and b) of paragraph 22, are entitled to a filing date of 30 August 1983 and that other claims are entitled to the filing date of the instant application, namely, 2 June 1995. With respect, we consider this conclusion to be erroneous in the extreme.

First, the present application was filed in order to obtain benefit of filing date prior to the effective of the new GATT legislation which imposes the severity of term limitations. It was filed as a 37 CFR 1.60 continuation application and contains an identical disclosure as the parent applications from which it claims priority. As such, of course it should obtain benefit to the filing dates of the respective parent applications going back in time to the earliest filing date of 30 August 1983.

The logical consequences of the Examiner's conclusion are manifested in Paragraph 23 of the official action where certain of the present claims are rejected under 35 USC 102(b) as "being anticipated by Berman", a reference which did not appear in print until September of 1988. If the Examiner were to have thoroughly reviewed the content of the earlier parent applications, the Examiner would have found in the application filed first on 30 August 1983 namely Serial No. 06/527917 full support in all respects of the subject matter claimed herein. In said earliest application there are working examples directed to the preparation

of the full length and C-truncated versions of the gD glycoprotein of herpes simples virus 1 together with full *in vivo* animal challenge data demonstrating successful utility as a vaccine. That application further provides generic support for the preparation of vaccines based upon membrane-bound polypeptides associated generally with "pathogenic organisms" of which herpes virus is set forth merely by way of an example. We direct the Examiner's attention to the discussion *supra* which provides more information in this regard with respect to chapter and verse.

The second application in this series that was filed on 31 October 1983, USSN 06/547551, contains an identical disclosure and in addition provides working examples directed to the use of the disclosed vaccines as successful in *in vivo* animal challenge against HSV-2 pathogen.

The third and last (in terms of disclosure content) application in this series, filed on 9 March 1984, USSN 06/588170, supplied working examples of the gC glycoprotein of HSV-2. Importantly, all of these earlier applications antedate the publication date of the Berman reference, and as such, the Berman reference simply is no where near qualified under 35 USC 102(b) given that its publication date at least four years subsequent to the priority date to which the present claims are unassailably availing of priority.

We note the comment with respect to paragraph 24 of Paper No. 4

***The Rejection under 35 U.S.C. § 103 (Paragraph 25 of Paper No. 4)***

Claims 1 to 4, 6, 7, 10, 11, 13 to 15, 18 and 19 stand rejected under 35 U.S.C. § 103 as purportedly "being unpatentable over Watson et al., 1982 in view of Rose et al., 1982". Specifically, the Examiner states that Watson et al. "teach the cloning and expression of the gene coding for herpes simplex virus type 1 glycoprotein D", that "glycoprotein D is capable of generating antiserum which can neutralize infectivity of herpes simplex virus (HSV) types 1 and 2" and that the "antiserum generated to the glycoprotein D protected mice from neurological disease," and that they "appear to describe a truncated gD glycoprotein." The Examiner further states that Rose et al. teach the expression of a cell surface secreted form of the vesicular stomatitis virus G protein.

Given the above, the Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the Watson et al. and Rose et al. articles to obtain a membrane-bound or secreted form of glycoprotein D which would be expected to be an effective vaccine when administered. Applicants respectfully traverse.

Initially, with regard to the Watson et al. *Science* article, the Examiner first states that "Watson teach the cloning and expressions [sic, expression] of the gene coding for herpes simplex virus type 1 glycoprotein D". However, a detailed reading of the Watson et al. article

indicates that while Watson et al. do provide the nucleotide sequence of the HSV-1 coding region, the only proteins expressed are fusion proteins which also contain amino acid sequences derived from the bacteriophage λCRO protein. Thus, contrary to the Examiner's implication herein, Watson et al. do not express nor produce the complete, intact and unassociated glycoprotein D molecule.

The Examiner next states Watson et al. teach that:

> "glycoprotein D is capable of generating antiserum which can neutralize infectivity of herpes simplex virus (HSV) type 1 and type 2. In vivo antiserum generated to the glycoprotein D protected mice from neurological disease induced by either HSV type 1 or type 2 (page 381)".

Again, this statement is extremely misleading and is incorrect in fact. First, none of the above was actually demonstrated by Watson et al. Watson et al. merely make reference to such work in the "background" section of their article. As such, Watson et al. cannot be credited with "teaching" the above.

Next, while Watson et al. do indicate that antiserum to various herpes glycoproteins can neutralize infectivity by HSV in vitro, nowhere in the Watson et al. article is it demonstrated that antiserum produced in vivo is capable of neutralizing HSV infectivity in vivo. The Examiner's statement reproduced above (citing to page 381 of the Watson et al. article) implies that antiserum directed against gD was produced in vivo and was shown to be capable of neutralizing HSV infectivity in vivo. This is absolutely incorrect. A detailed reading of the section cited by the

Examiner indicates that monoclonal antibodies directed against the gD protein were obtained and the monoclonal antibodies themselves were passively transferred into mice. Thus, no antiserum was produced against the gD protein in vivo nor was any anti-gD antiserum tested for it ability to neutralize HSV infectivity in vivo.

The Examiner also states that "Watson et al. appear to describe a truncated gD glycoprotein". Again, this implication is incorrect. As described above, Watson et al. describe the construction and expression of fusion proteins only. Nowhere in the Watson et al. article are unassociated, truncated forms of the gD polypeptide produced or expressed.

In the prosecution of a parent application herein, namely, Serial No. 07/814,243 in an amendment filed by mailing on 19 April 1993, Applicants pointed out that the so-called Watson et al. art should include not only the *Science* article cited by the Examiner herein but also two Watson patents (US 4,818,694 and 4,891,315). In an amendment filed on or about 10 November 1993 in that case, referring to an interview extended to Applicants' representatives on 28 October 1993, we pointed out that the three Watson et al. references were discussed therein. Previously, and herein, we refer to all of these references as the "collective Watson references."

With particular reference to the Watson '315 patent, we note that although it contains a first filing date in the United States of 20 July

1982, there were also two continuations-in-part filed resulting in a final application filed 6 July 1983, i.e., just closely prior to the effective filing date herein of 30 August 1983. I have been informed, and believe, that the continuation-in-part applications added substantial subject matter. I draw particular attention to the subject matter in columns 43 and 44, and in particular Tables 4 and 5 that were added by the application filed on 6 July 1983. Certain other subject matter takes only the 25 October 1982 date.

In previous responses to Office Actions in applications throughout the lineage of the present application, Applicants have pointed out that the Watson et al. *Science* article provides absolutely no challenge data. (The Science article is the reference used as a basis for this rejection). This is significant because Applicants have demonstrated herein the provision of an absolute protective effect upon challenge, which is the hallmark, indeed the necessity, of a vaccine that could expect to be ultimately commercially successful. For example, Applicants have pointed out in previous applications in the lineage herein the "unexpected results" demonstrated by the present application and have compared those unexpected results to the results of the collective Watson references. Applicants have pointed out that the present invention provides 100% effectiveness against the challenge of herpes simplex virus (HSV) at 100 to 500 times $LD_{50}$, whereas the fusion polypeptides of the Watson '315 patent provided only 30 to 80% survival against the challenge of 10 to 17

times $LD_{50}$. Applicants have argued, we believe with correctness, that these were unexpected results clearly evidencing the non-obviousness of the presently claimed invention.

In regard to the unexpected nature of the results presented herein, the Examiner is directed to page 28 and 31 of the present specification, Tables 1 and 2, where it is clearly shown that the truncated antigen provides complete effectiveness after immunization followed by challenge. Of the 11 mice treated, 11 survived and zero were dead. Of the control mice, three were paralyzed, seven were dead and three survived. It was stated that the significance of this data stood at the $p = 0.002$ level. Similarly in a second study represented by Table 2, again the vaccine of the present invention provided a 100% protection against challenge, the necessity of a vaccine.

Similarly on page 20 of the specification where mice were immunized with the full-length vaccine of the present invention, all of the mice in the control group died while all of the experimental mice were protected and showed no sign of infection. Thus, the specification itself fully supports the unexpected results of the present invention by this data alone. Applicants iterate that for a vaccine to be truly a vaccine, it must provide 100% protection. Contrast this with the data of the '315 Watson reference where they achieved no more than 80% protection with far less $LD_{50}$ challenge, surely results defining failure as a vaccine. Thus,

Applicants have herein provided an effective vaccine, something that the Watson art has failed to demonstrate.

Moreover, Applicants believe that a review of what the Watson et al. researchers themselves actually thought of their experimental work would be instructive on the question of unobviousness. In this regard, we refer the Examiner to the subsequently published article by these researchers namely Weis et al., *Nature* 302:72-74 (1983) which is enclosed herewith as Exhibit A. The Watson (Weis) *Nature* reference represents a disclosure of a continuation of the earlier reported research in the cited Watson *Science* article. In the *Nature* article, the same authors describe the construction of a hybrid gene encoding again a chimeric protein, not a gD, not a truncated gD, containing HSV-1 gD, bacterial phage λCRO and E. coli β-galactosidase protein. They claim that the expedient of including the β-galactosidase portion provided higher levels of expression of the chimeric product in E. coli. They go on to say that the chimeric protein elicits antibodies in rabbits to provide neutralization in vitro. It is emphasized that this does not amount to an in vivo challenge which is the premise of the present invention as embodied by the presently pending claims.

Turning to page 74, left column of the *Nature* article, in the only complete paragraph, it is interesting to note how the authors themselves characterize their work. They state, "[t]he results presented here demonstrate the feasibility of producing a sub-unit vaccine against HSV-1

and HSV-2 using recombinant DNA techniques." (Emphasis supplied). Of course, that "feasibility" does not equate to success of actually producing an in vivo vaccine effective against challenge by virus.

Further down in the paragraph in the left column on page 74 of the *Nature* article, the authors indicate that the chimeric protein they produced was "capable of neutralizing...in vitro." Then they make the very telling admission that "[e]xperiments are now in progress to determine whether vaccination with the chimeric protein is capable of protecting experimental animals from HSV challenge." (Emphasis supplied). Thus, the very same authors themselves admit that it can not be predicted that their chimeric material would prove to be an effective vaccine.

Applicants believe this to be a telling comment by the very authors on which the Examiner bases her rejections. As we have noted herein, when the Watson authors finally did their challenge work, much later - see the '315 patent referred to earlier - they found at best 80% protection, a result clearly incapable of proving an effective vaccine. Thus, while the Watson et al. authors would eagerly test their hypothesis, at the end of the day they did not achieve success as did the inventors of the present invention. We say that this itself is compelling evidence of unobviousness of the present invention in light of the collective Watson references.

The Rose et al. article cited herein describes the gG protein of VSV. The Rose et al. gG protein was a truncated version, and Rose

clearly states that the folding pattern of their material was unlike native protein. Applicants argue, therefore, that antibodies generated against this peculiarly folded truncated protein may or may not be generated and bind against the native protein because the peculiarly folded truncated protein would be expected to display a different secondary structure from the native protein. Therefore, if anything, the Rose et al. findings support our position that the truncated material of the present invention provided unexpected results.

In summary, the prior art cited by the Examiner herein simply does not support the position that the results presented in the present application would be reasonably expected. Applicants have pointed out that the fusion polypeptides of the collective Watson references failed to give adequate protective results for purposes of producing and using a vaccine. Applicants also submit that the Rose et al. art simply underscores our position that it would be unexpected that a truncated version of a given antigen would be successful to provide 100% protection on challenge, i.e., an effective vaccine. As such, the combination of the Watson et al. art with Rose et al. does not provide the suggestion or reasonable expectation of success required to support a rejection under 35 U.S.C. § 103. The rejection should, therefore, be withdrawn.

We believe that the above remarks serve to place the present application in an obvious condition of allowability, both as to formal matters (e.g. the correction of typographical error in the specification and

the elimination of rejection under 35 USC 101 and 112) and as to substantive matters based upon the prior art cited under 35 USC 103.

Applicants wish to inform the record of the substantial prosecution history of this application via the several patent applications in historical priority lineage with the present application. During the course of that prosecution which has already consumed many years, the substantive issues currently raised in Paper No. 4 have been previously raised, and we believe, completely and thoroughly rebutted, not only with legal arguments but with factual distinctions over the art upon which the rejections are based, coupled with the filing of several affidavits from persons of skill in the art of immunology as well as business officials who have attested to the secondary considerations that must be considered on questions of patentability.

We respectfully point to our belief that the record of the parent applications via the present application is already sufficiently developed so that one could not but be led to a conclusion that patentable subject matter is certainly represented by the present claims.

Therefore, we respectfully request the review of such previous prosecution record, and by these remarks specifically incorporate by reference all of such prosecution history into the record of the present application. In particular we refer to the most immediate parent application hereof, USSN 08/357,084 filed 15 December 1994 in which such prosecution was laboriously developed and filed including

declarations by Drs. Skehel, Secher and Rose demonstrating factual evidence that established that at the time the present invention was made, scientific peers not associated with the inventors hereof could not have reasonably predicted success, but that after the fact of success of this invention as set forth in the present specification and claims, the invention was newly predictive of operability for similar type vaccine production over a wide pathogenic host range. In addition, we have traced the history of vaccine development, reviewed the disclosure of the collective Watson references and provided distinctions that the present invention has over the publications used as the basis for substantive patentability rejections herein. We adduced evidence of secondary considerations mandatory for review in determinations on the issue of patentability.

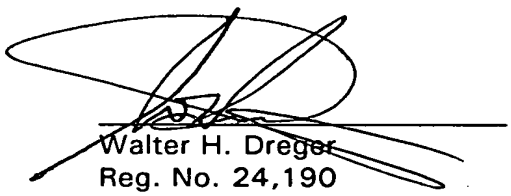
In addition, we forwarded the decision of the Opposition Division of the European Patent Office for the European counterpart of the present invention wherein said Opposition Division found for patentees on questions of novelty, obviousness and enablement. We pointed out as well the judicial authority in this country that suggests that such decisions of foreign examining authorities should be taken as evidence probative on questions of patentability.

In short we have already adduced a copious review of the cited art and have summarized in considerable detail our arguments that we believe unequivocally establish patentability of the claimed subject matter. From

all of this prosecution history we believe that it must be concluded that the review of patentability standards for the present claimed subject matter has been thorough and complete enough to induce the Patent Office's production of an official notice of allowance. We respectfully request this.

Respectfully submitted,

FLEHR, HOHBACH, TEST,
ALBRITTON & HERBERT



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